REMARKS

The Office action mailed 26 August 2003, has been received and its contents carefully noted. Claims 4, 11, 12, 18, 22-25, 29 and 30 were pending. By this amendment, claim 18 has been canceled and claims 4, 12, 22-25, and 30 have been amended and new claim 31 has been added. Support may be found in the specification generally and the claims as originally filed. No statutory new matter has been added. Therefore, entry of the claims as amended is respectfully requested.

Rejection under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 18 and 22-25 under 35 U.S.C. 112, first paragraph, as being nonenabled for a vaccine or a pharmaceutical composition.

Applicants respectfully submit that the claims as amended obviate the rejection. Therefore, the rejection under 35 U.S.C. 112, first paragraph, should properly be withdrawn.

Rejection under 35 U.S.C. 112, second paragraph

The Examiner rejected claim 4 under 35 U.S.C. 112, second paragraph, as being indefinite as the Examiner deemed it was not clear whether "at least one Leishmania parasite" referred to "one parasite" or "one strain of the parasite".

Applicants respectfully submit that the claim as amended makes clear that at least one Leishmania parasite strain is microfluidized. Therefore, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

Rejection under 35 U.S.C. 102(b)

The Examiner rejected the claims under 35 U.S.C. 102(b) as being anticipated by Leishmania Research Project DOD-8b (DOD-8b), Stitler et al. (1994), and Stitler et al. (1995). Specifically, the Examiner deemed that DOD-8b, Stitler et al. (1994), and Stitler et al. (1995) teach a microfluidized lysate preparation and that since the USPTO does not have the facilities for comparing the prior art preparation with the claimed preparation, the Applicant has the burden to show the novel or unobvious differences.

Applicants respectfully submit that the microfluidized lysate preparations of DOD-8b, Stitler et al. (1994) and Stitler et al. (1995) are first generation preparations (MFL-LSTA-Lt).

The microfluidized lysate preparation of the present invention is a second generation preparation (alternatively referred to herein as MFL-LSTA-R2, MFL-LSTA *L. mexicana*, MFL-LSTA *L. guyanensis*).

The first generation and second generation preparations are significantly different. Phase 1 of clinical studies show that the MFL-LSTA-Lt (Lot No. 0172), a microfluidized product made from a *L. tropica* strain containing Tween-80® and dextran, was toxic. This lot was tested in ten Leishmania naïve individuals in a safety and sensitization study at WRAIR during 1997-1998. The volunteers received 4 doses (two weeks apart) of the MFL-LSTA-Lt (0.1 ml intradermal/ ID) in an escalating dose regimen to assess safety. The total protein concentration per dose was respectively: 0.25 μg-first, 2.5ug second, 8 μg-third, and 25 μg-fourth. The volunteers then received three additional 25 μg doses of antigen at two-week intervals to evaluate sensitization.

The MFL-LSTA-Lt was safe at the highest dose (25 μg protein) in only 6 of 10 volunteers. One volunteer developed clear rhinorrhea and nasal pruritus within minutes of receiving the first dose followed by transient urticaria at the test and control-diluent sites four hours later. This reaction was consistent with systemic manifestations of type I hypersensitivity, and it was concluded that the reactions were most likely related to the presence of Dextran T-10 i and the diluent control. See Specification on page 17, paragraph 63. Three additional volunteers were dropped from the study, one following the second dose and two following the third dose, after developing induration at the LSTA site. One volunteer completed 5 doses of antigen, two at the 25 μg level, without difficulty but withdrew from the study due to a move out of the area. Five remaining volunteers completed all seven doses of antigen without sequelae.

Due to the apparent sensitization, the *Leishmania tropica* skin test was reformulated by eliminating the freeze-dry components (Dextran T-10 and Sucrose) as well as the freeze-dry procedure in the reformulated MFL-LSTA-R2. The strategy in the reformulation was to replace the lyophilization storage of the final product stabilized with Dextran, with a final product stabilized in a liquid formulation which included 0.4% Phenol as a preservative. The batch production records (BPRs) were rewritten, process steps deleted and other added, antigens centrifuged, antigens treated at high temperature to denature proteolitic enzymes, the product filtered, and the testing changed because they are different antigens/products, i.e. new antigens. This reformulated MFL-LSTA-R2 was well tolerated (no evidence of major systemic or DTH

reactions) as a single injection in 15 out of 15 volunteers at doses of 0.38 μg, 3.8 μg, and 38 μg in a Phase 1 clinical study conducted.

Applicants respectfully submit that the cited prior art only discloses the general procedures for making the first generation lysate preparations. Nowhere do the cited prior art teach or suggest microfluidized lysate preparations that are free of dextran. The absence of dextran is important as a subject who had never been previously exposed to a Leishmania parasite, may exhibit a type I hypersensitivity reaction which may be incorrectly interpreted as a positive reaction indicating exposure to a Leishmania parasite. Nowhere do the cited prior art teach or suggest a microfluidized lysate preparation that is suitable for reliable assays, i.e. little to no false positives. Nowhere in the cited prior art is a microfluidized Leishmania lysate preparation free of dextran disclosed or suggested.

Since the cited prior art do not teach or suggest a microfluidized lysate preparation free of dextran made by microfluidizing a slurry of at least one *Leishmania* parasite strain through a chamber and disrupting the leishmania parasite strain with a sudden release of pressure, the microfluidized lysate preparation as claimed is novel and unobvious. Therefore, the rejection under 35 U.S.C. 102(b) should properly be withdrawn.

Invention Disclosure Statement

Applicants resubmit herewith the Invention Disclosure Statement, PTO Form 1449, and copies of references that were previously submitted on 25 September 2002, for proper consideration. Acknowledgement of receipt is respectfully requested.

Request for an Interview

Should there by any remaining issues after entry of the amendment and consideration of the remarks herein, Applicants respectfully request either an in-person interview or a telephonic interview with the Examiner.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. If, however, extensions of time under 37 C.F.R. §1.136 other than those otherwise provided for herewith are required to prevent abandonment of the present patent application, then such extensions of time are hereby petitioned, and any fees therefor are hereby authorized to be charged to our Deposit Account No. 210-380, Attorney Docket No. 034047.013US (WRAIR 98-40/46) (formerly P66822US0).

Respectfully submitted,
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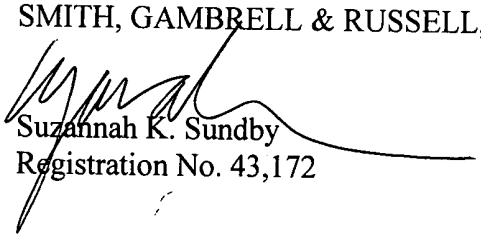

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Date: 25 November 2003

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